Notice of Allowability	Application No.	Applicant(s)	
	10/593,831	AKAIKE ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *9/21/2010*.

2. ☒ The allowed claim(s) is/are *1,2,5-9 and 13-18*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 9/22/2006
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20100930* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/SCOTT LONG/
Primary Examiner, Art Unit 1633

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 4 October 2010.

Restriction

The examiner hereby withdraws the restriction requirement, filed 1/5/2009. The examiner rejoins the withdrawn claims.

RESPONSE TO ARGUMENTS

35 USC § 102

The rejection of claims 1, 3 and 9 under 35 USC 102(b) as being anticipated by Xu et al. (Nature Biotechnology. October 2001; 19: 971-974) is withdrawn in response to the applicants arguments and/or claim amendments. The applicant's arguments have been fully considered and are persuasive. The applicant has amended the claims to introduce the limitation, "cadherin molecule [immobilized or coated on a substrate]." This claim amendment narrows the scope of the claims and Xu does not teach this limitation. Therefore, the examiner hereby withdraws the rejection of claims 1, 3 and 9 under 35 U.S.C. 102(b) as being anticipate by Xu et al. (Nature Biotechnology. October 2001; 19: 971-974).

35 USC § 103

The rejection of claims 1, 3-9 and 19-20 under 35 USC 103(a) as being unpatentable over Nagaoka et al (Biotechnology Letters, 2002; 24: 1857-1862) [known hereinafter as Nagaoka1] and in view of Nagaoka et al. (Cell Structure and Function, 2003; 28(4): 327, IP-53) [known hereinafter as Nagaoka2] and further in view of Alonso et al. (Int. J. Dev. Biol. 1991; 389-397) is withdrawn in response to the applicants arguments and/or claim amendments.

The applicant's arguments and claim amendments have been fully considered and are persuasive. The applicant has amended the claims to introduce the limitation, "cadherin molecule [immobilized or coated on a substrate]," and "wherein said pluripotent stem cells achieve cell counts at least about two time greater than said pluripotent stem cells cultured on a gelatin plate after four days." The applicant has argued that the cited references do not teach or suggest the property of (greater cell proliferation) producing a greater number of cells on the cadherin-coated culture plates than conventional gelatin plates (Remarks, filed 9/21/2010, page 7). The examiner accepts these claim amendments and arguments.

Therefore, the examiner hereby withdraws the rejection of claims 1, 3-9 and 18-19 under 35 USC 103(a) as being obvious over Nagaoka1 et al and Nagaoka2 and Alonso.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Robert Lampe on 10/11/2010.

The claims have been amended as follows:

1. (Amended) A method for growing pluripotent stem cells which exhibit a normal karyotype comprising contacting said pluripotent stem cells with a liquid medium and growing said pluripotent stem cells in said liquid medium in a dispersed state in a culturing vessel without using feeder cells, wherein said pluripotent stem cells maintain their undifferentiated state and pluripotency, said culturing vessel including immobilized or coated on a substrate solid phase surface a cadherin molecule, and wherein said pluripotent stem cells achieve cell counts at least ~~about~~ two times greater than said pluripotent stem cells cultured on a gelatin plate after four days.

2. (Amended) The method of claim 1, ~~wherein said growing step is followed by~~ further comprising transferring a gene into said pluripotent stem cells, after culturing.

Claims 11-12 are cancelled.

13. (Amended) The method of claim 2 ~~claim 12~~, wherein said cadherin molecule ~~belonging to the cadherin family~~ is E-cadherin, or a molecule which has structure homology with said molecule, which comprises the EC1 domain and one or more domains from the EC2 domain, EC3 domain, EC4 domain and EC5 domain of E-cadherin, and which has homophilic binding ability with said pluripotent stem cells.

14. (Amended) The method of claim 13, wherein said E-cadherin is mammalian ~~obtained from a mammal~~.

15. (Amended) The method of claim 14, wherein said E-cadherin is ~~obtained from a~~ human or mouse.

16. (amended) The method of claim 2, wherein said cadherin molecule ~~the molecule which is adhesive to said pluripotent stem cells~~ is fused with an immunoglobulin Fc region and is immobilized on said substrate solid phase surface *via* said Fc region.

18. (Amended) The method of claim 2, wherein said cadherin molecule ~~the molecule which is adhesive to said pluripotent stem cells~~ is a human or a mouse E-cadherin ~~obtained from a human or mouse~~ and said pluripotent stem cells are mammalian embryonic stem cells (ES cells).

Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

The prosecution history provides evidence for allowability.

The prior art does not disclose culturing dispersed, pluripotent stem cells on cadherin-coated plates, resulting maintenance of undifferentiated state and pluripotency, and proliferation of pluripotent stem cells such that after 4 days of said culture, there are about a two times greater amount of pluripotent stem cells produced when compared to said pluripotent stem cells are cultured for four days on a gelatin plate. Song et al. (PNAS. 12 Nov 2002; 99(23): 14813-14818) demonstrates cadherin-mediated cell adhesion is essential for maintenance and proliferation of somatic stem cells in their niches. However, Song et al. does not extrapolate their findings into methods of culturing pluripotent stem cells and provides no evidence that suggests that dispersed pluripotent stem cells could be proliferated in feeder cell-free, cadherin-coated culture system. Additionally, Fuchs et al. (Cell. 19 March 2004; 116: 769-778) teach that *in vivo* stem cell numbers increase based upon their ability to adhere through N-cadherin-mediated junctions (page 771, col.1, 2nd paragraph). While Fuchs et al. indicate that embryonic stem cells can be cultured indefinitely in tissue culture without losing their pluripotency, Fuchs does not guide a skilled artisan to culture pluripotent stem cells in a feeder cell-free, cadherin-coated culture system. Various cell lines have been cultured on cadherin-coated plates, but none of prior art which cultures (tumor) cell lines on cadherin-coated plates utilizes a cell line that is a model of stem cells (e.g.,

Hurt et al. (Cancer Cell. Feb 2004; 5: 191-199)). Giesberts et al. (Mechanisms of Development. 1999; 83: 115-125) teach that human embryonal carcinoma cells (a cancer cell line used as a model of human stem cells) express many types cadherins. However, Giesberts et al. teach that "cadherin-mediated cell adhesion does not appear to play a role in maintaining an EC [human embryonal carcinoma] phenotype" (abstract). Therefore, there is ample suggestion in the prior art that stem cells cultured in feeder-cell free cadherin-coated plates would have resulted in formation of embryoid bodies or resulted in a differentiated phenotype.

Accordingly, the examiner concludes a skilled artisan aware of the approaches used at the time of filing, would NOT have proposed culturing dispersed, pluripotent stem cells on cadherin-coated plates, resulting maintenance of undifferentiated state and pluripotency, and proliferation of pluripotent stem cells such that after 4 days of said culture, there are about a two times greater amount of pluripotent stem cells produced when compared to said pluripotent stem cells are cultured for four days on a gelatin plate.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 1, 2, 5-9, 13-18 are allowed. Claims 3-4, 10-12, 19-20 are cancelled.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SCOTT LONG/
Primary Examiner, Art Unit 1633